REMARKS

Claim 19 is the only pending claim for examination. Claim 19 is not amended herewith. No new matter has been added.

Double Patenting Rejection

Claim 19 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-11 and 13-30 of copending application No. 09/818918. Applicants defer substantive rebuttal until the above-identified conflicting claims are allowed.

Rejections under 35 U.S.C. §112

The Examiner rejected claim 19 under 35 U.S.C. §112 for lack of enablement commensurate in scope with the claimed invention. The Examiner indicated that the specification, while enabling a method for treating asthma using a particular CpG oligonucleotide (SEQ ID NO:10), did not enable a method of treating an allergic response or allergy related disorder using a CpG oligonucleotide with any size or formula. *See* the Office Action, pgs 3-4. The Examiner further concluded that undue experimentation would be required for a skilled person in the pertinent art to make and use the claimed invention. *Id.*, pg 9. In particular, the Examiner pointed out that the state of the art was unpredictable with regard to the use of CpG oligonucleotides in treating allergic disorders, *Id.*, pg 4, and that the instant application failed to provide working examples, *Id.* pgs 10-11.

Applicants respectfully request reconsideration for the reasons set forth below.

Claim 19, the only pending claim, is directed to a method for treating an allergic response to an antigen or allergy related disorder during antigen specific immunotherapy of a subject comprising administering to the subject a first composition comprising a 5'CpG3' immunostimulatory oligonucleotide and a second composition comprising an antigen. The CpG oligonucleotide can inhibit the allergic response in the subject and, together with the antigen, can modulate the immune response to the antigen.

The enablement requirement under 35 U.S.C §112 inquires whether the application, when filed, contained sufficient information to enable one skilled in the pertinent art to make and use

the claimed invention commensurate in scope with the claims without undue experimentation. *See* MPEP 2164.01. Applicants herewith submit that the reasons proffered in the Office Action are not sufficient to support that undue experimentation is required for a skilled person in the art to make and use the claimed invention.

First, several papers were cited to support the lack of enablement rejection and, in particular, to support the argument that the state of the art is unpredictable with regard to the use of CpG oligonucleotides for treating allergy. *See* the Office Action, pgs 4-10. Applicants respectfully traverse.

McCluskie et al., 1999 and Krieg et al., 2000 were cited for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism.

McCluskie et al. discloses the induction of antigen-specific immune responses by a DNA plasmid encoding hepatitis B surface antigen (HBsAg). The claimed invention encompasses the use of a CpG oligonucleotide. Since the issues of predictability and therapeutic effectivity are very different for CpG oligonucleotides and DNA plasmids encoding antigens, the teaching in McCluskie et al. is irrelevant to the enablement requirement of the instant application. Please note that on page 296 as identified by the Examiner, McCluskie et al. recognizes that the CpG motif can influence the Th bias in a recipient. This teaching is consistent with the disclosure in the instant application.

Krieg et al. is a review article describing the uses of CpG oligonucleotides. Applicant cannot locate the teaching that "bioresponses to the administration of CpG vary depending on the mode of administration and the organism" on page 524, to which the Office Action specifically pointed. In fact, Krieg et al. teaches that synthetic CpG oligonucleotides, by inducing Th1-biased immune responses, have shown significant effects as vaccine adjuvants and as immunotherapeutics for treatment of cancer and allergic conditions in model systems. *See* the Abstract. It further teaches that "the potent Th1 adjuvant effect of CpG DNA can even override preexisting Th2 immune responses; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation." *See* pg 524. In sum, the teaching of Krieg et al. does not cast doubt on the enablement of the claimed invention.

The Examiner has cited Wohlleben et al. 2000 to support the arguments that (1) "the state of the art questions whether 'CpG-ODNs' can be used in humans to inhibit the development of asthma, and that (2) "all approaches that induce Th1 responses have the potential side-effects of Th1 cell-mediated inflammation potentially causing serious tissue damage." *See* the Office Action, pgs 5-6.

Applicants respectfully disagree with the Examiner's understanding of Wohlleben et al. In fact, Wohlleben et al. provides a favorable view of CpG oligonucleotides and their usefulness in treating asthma. The use of CpG oligonucleotides is identified in the abstract and conclusion of the paper as one of "the most promising approaches" for the treatment of atopic diseases and particularly asthma. Even the cited paragraph on page 620 relates to the expectation that CpG oligonucleotides will be effective in humans. For example, it teaches that the "results obtained from animal models suggest that it is *probable* that these approaches might also be successful in humans to reduce the development of atopic disorders." *See* pg 620, 2nd para. It further teaches that "[t]his suggests that the treatment of humans with CpG-ODNs could be very effective in inhibiting the development of asthma." *See* pg 620, Col. 2, 1st para. Taken together, the teachings found in Wohlleben et al. do not support the conclusion that the claimed invention was not enabled at the time the instant application was filed.

Further, the teachings of Wohlleben et al. with respect to potential harmful side effects do not support a lack of enablement of the pending claims. MPEP 2164.01(c) has made it clear that an applicant need not demonstrate that his invention is safe. Thus, whether a drug is safe or has no harmful side effects is not an appropriate test for enablement. In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial. However, the law is well established that a clinical trial is not required for enablement. Additionally, Wohlleben et al. does not provide sufficient evidence showing that CpG-ODNs would cause harmful side effects when applied in humans. To the contrary, on page 620 immediately following the discussion of side effects, Wohlleben et al. states that "it is totally unclear if this can also occur in healthy rodents or, more importantly, humans." *See* pg 620, Col. 2, 1st para.

Satoh et al. was also cited to demonstrate that CpG was associated with dangerous side effects. This reference is an abstract describing a study on the effects of CpG oligonucleotides administered subcutaneously to mice that are treated with DNFB. It was concluded that CpG oligonucleotides were responsible for worsening of the allergic contact dermatitis (ACD)

induced by DNFB. As mentioned above with respect to Wohlleben et al, the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. Additionally, the teachings of the Satoh et al reference are not sufficient to establish a lack of enablement for the claimed invention. Note that the ACD is in fact caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB.

The Examiner further cited Kline et al., 2002, and Kline et al., 1998 to demonstrate that in some instances, the use of CpG alone is ineffective for the treatment of asthma. In particular, the Examiner asserted that Kline et al., 2002, disclosed that "a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model." The section of the paper identified by the Examiner on page L172 relates to an experiment designed to model "persistent asthma in humans, who, by current standards of treatment, require intensive anti-inflammatory therapy." The claimed invention does not require that the persistent asthma be treated with a single dose of CpG. Doses are within the purview of those skilled in the art, and the data in Kline et al., 2002, supports that monotherapy at appropriate doses can work. As a matter of fact, many drugs, including those for treating chronic asthma, are not effective when used as a single dose. Therefore, the fact that a single dose of CpG is ineffective does not negate the conclusion that CpG ODN is a promising approach for treating asthma and allergy. Additionally, the claimed invention is directed to the use of a combination of CpG and antigen.

The Examiner has also indicated that Kline 2002 teaches that "splenocytes from OVA-treated mice did not develop an antigen specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophila, serum IgE and bronchial hyperreactivity (p. L176, col. 2)." *See* the Office Action, pg5. This statement does not support a lack of enablement of the claimed invention. The failure to develop a Th1 phenotype in mice in response to OVA treatment is not inconsistent with the invention. The second sentence is consistent with and even supportive of the utility of the invention.

Weiner is cited for the proposition that the molecular mechanism of CpG is unknown. However, knowledge of the mechanism of a claimed invention is not a prerequisite for its patentability. *See* Newman v. Quigg, 877 F.2d 1575, 1581. The instant application identifies

consistent changes in the immune system at the cellular level in response to CpG administration. These immune responses are therapeutically relevant. Additionally, Table 1 of Weiner lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with enablement of the claimed invention. For instance, it teaches that "[s]tudies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." *See* pg 456, 1st column. In addition, page 457 under "In vivo effects of CpG ODN" shows that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

Agrawal et al has been cited in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable. In particular, the examiner has identified pages 78-80 as being particularly relevant. Agrawal et al is a review article describing antisense oligonucleotides. The authors suggest on page 78 that in order to *reduce* non-antisense related activity, it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification, however, teaches that a CpG containing oligonucleotide has *an unmethylated C* in the CpG motif. Further, the cited section of Agrawal et al teaches that the proposed modifications "significantly reduced side effects". Thus, Agrawal et al does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced.

The Examiner has cited Hussain et al., 2004, to support the proposition that "combined data from our studies with the murine model of allergic rhinitis and limited data from skin favor the idea that CpG ODN may be an attractive therapy in the treatment of acute atopic dermatitis." *See* the Office Action, pg 6. This statement supports the enablement of the claimed invention. The Examiner further cited Leung, 1999, to demonstrate that "the long-term benefits of treatment with CpG ODN remain speculative." *Id.* Applicant cannot locate this reference because the full citation thereof has not been provided in the Office Action or PTO Form 892. Thus, no comments can be made at this time.

The Examiner has also cited Dziadzio et al. to support the statement that the state of the art is "unpredictable with regard to the use of ISS-ODN in treating asthma." *See* the Office Action, pg 6. However, Dziadzio et al. actually teaches that CpG containing oligonucleotides are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, Dziadzio et al teach:

> "These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease." (page 280, 2nd-3rd full paragraphs).

The teachings of Dziadzio et al. as a whole do not support a finding that the claimed invention was unpredictable at the time of filing the instant application.

Metzger et al., 1999, is cited to show that "oligonucleotide therapy for asthma seems unlimited, but confirmation awaits the extension for animal models to human studies." *See* the Office Action, pg 7. This reference summarizes methods of oligonucleotide therapy of allergic asthma, including DNA vaccination with CpG DNA as a vaccine adjuvant. It teaches that "CpG DNA not only promotes nonspecific innate immunity but also generates antigen-specific immune responses" and that "[t]hey have been described to be actually more potent than Freund's adjuvant in producing TH1-like vaccine responses." *See* pg 264, col. 1. Thus, the teaching of Metzger as a whole, also does not support the finding that the claimed invention was unpredictable at the time of filing this application.

The Examiner has cited Van Uden et al for the concept that each ISS has a minimum length limitation and that potential side effects associated with treatment must be considered. With respect to the section of the paper that refers to the length of ODN, the authors do not conclude that there is a specific rule for the length of the ODN. The authors hypothesize that different lengths and flanking sequences have an impact on the activity of the ODN. The patent application as filed confirms that certain motifs and lengths are preferred. However, it is believed that most unmethylated CpG containing oligonucleotide within the scope of the claims

would have the ability to induce *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response when administered in an appropriate dosage.

The examiner quotes some language from page 907 column 2 and page 908 column 1 related to the issue of side effects associated with CpG oligonucleotide administration. Again, as noted above, safety is beyond the standard of the enablement requirement. *See* MPEP 2164.01(c). In addition, each of these statements, however, is taken out of context. After the quoted section the authors point out that such side effects have not been observed. For example, the Examiner has pointed to the statement on page 907 that "[t]here is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers" and compared the effects of CpG with LPS. *See* the Office Action, pg 8. In contrast to the implications from the language quoted in the office action, immediately following that paragraph the authors conclude

> "Although these reports demonstrate the possibility of shock in extreme cases of sensitization or concurrent LPS exposure, there has never been a reported case of ISS alone causing shock in any kind of healthy animal at any dose." (Page 908 column 1 lines 2-6) and
> "We and others have never observed gross inflammation in response to ISS in ODN or plasmid form in any experimental animals or humans." (page 908 first column first full paragraph)

The Examiner has also stated that Van Uden et al teaches that "ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA." In contrast to this statement, the authors point out an experiment in which bacterial DNA complexed with CFA is injected into mice. It is concluded that

> "When the mixture is given to preautoimmune NZB/NZW F1 mice, they develop antibodies that cross-react with mammalian DNA, but surprisingly they are actually protected from their spontaneous autoimmune disease. There still are no examples of ISS directly causing any type of autoimmune disease in animal models." (page 908 paragraph bridging columns 1 and 2).

Accordingly, Van Uden et al. does not provide sufficient evidence showing that CpG ODN is unsafe when applied in humans.

The Examiner has cited Kussebi to show that "in general, the direct conjugation of CpG-ODNs to allergenic proteins or peptides was more effective than their co-administration, possibly because of enhanced interaction with dendritic cells via the CpG moiety (p. 300, col. 1)." *See* the Office Action, pg 8. The claims are not limited by whether the ODN and antigen are

conjugated. Thus, the claims encompass administration of ODN and antigen, whether conjugated or not. Additionally, the above statement does not deny CpG's effects of inducing immune responses when co-administered with allergenic proteins. To be patentable, an invention need not be superior than any known relevant technology. *See* Custom Accessories v. Jeffrey-Allan Indus., 807 F.2d 955, 960 (Fed. Cir. 1986) ("Finding that an invention is an "improvement" is not a prerequisite to patentability. It is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability.")

Overall, the references cited by the Examiner are not sufficient to support the conclusion that the state of the art is unpredictable with regard to the use of CpG oligonucleotide in treating allergic disorders. To the contrary, these references provide numerous *in vitro* and *in vivo* data demonstrating that administration of CpG-ODNs is a promising approach to stimulate a Th1 response in the recipient and thus to treat diseases such as asthma and allergy.

Second, the Examiner stated that the specification, disclosing the use of a particular CpG oligonucleotide (SEQ ID NO:10) to treat asthma in a murine model, did not provide sufficient enablement for the claimed method – treating allergy by administering to a subject an immunostimulatory CpG oligonucleotide of any size and an antigen. *See* the Office Action, pg 3. Applicant respectfully disagrees.

The specification of the instant application has disclosed a class of oligonucleotides having a common motif, a CpG dinucleotide, that can produce a Th1 biased immune response. In particular, the CpG oligonucleotides can induce monocytic cells and other immune cells to produce Th1 cytokines, including IL-12, IFN-γ and GM-CSF. *See* pg 7, lines 15-17. To support this statement, the application has provided numerous data obtained both *in vivo* and *in vitro*, using an adequate number of different CpG-containing oligonucleotides (more than 40 oligonucleotides were tested). *See e.g.*, pg 20, Table 1, pg 21, Table 2 and pg 23, Table 3.

The data in the application, including that represented in Tables 1-3 establishes that the unmethylated CpG oligonucleotide is capable of inducing immune responses. The data in Table 5 demonstrates that the immune responses has the characteristic pattern of Th1 response. *See* pg 27. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating that CpG oligonucleotides can consistently drive the immune system toward a Th1 response. Pursuant to the data presented in the application, a skilled artisan would have recognized that many oligonucleotides containing the unmethylated CpG motif would be capable of invoking a Th1

immune response in a subject. In other words, the instant application is not limited to a particular CpG oligonucleotide, such as SEQ ID NO:10.

Pursuant to Chiron Corp. v. Genetech, Inc., 363 F.3d 1247, Applicant is not required to provide an example of using a CpG oligonucleotide of any size and formula to treat allergy, for the artisan's knowledge of prior art and routine experimentation can often fill gaps interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments.

Allergy is mediated by a Th2 immune response and a Th1 immune response is protective against allergy. *See* specification pg 41, lines 15-35. Thus a skilled person in the art would have acknowledged that redirecting a Th2 response to a Th1 response in a subject would be effective in treating or preventing allergy. In view of the above disclosure that CpG oligonucleotides are capable of invoking a Th1 response, it is predictable that CpG oligonucleotides, as recited in claim 19, can be used to treat and prevent allergy. In addition, the references cited by the Examiner also have demonstrated the promising effects of CpG oligonucleotides in treating allergy. The claimed invention is enabled because knowledge of the state of the art would allow one skilled in the art to extrapolate how to make and use the claimed invention from the disclosure of the instant application.

The Examiner also indicated that "the amount of direction or guidance presented in the specification and the presence or absence of working example is a hindrance to practicing the claimed invention." *See* the Office Action, pgs 8-9. Specifically, the Examiner pointed out that "the quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms, and further whereby treatment effects are provided for the claimed conditions." *Id*, pgs 9-10. Further, the Examiner stated that there was no working example provided in the instant application.

Applicant respectfully disagrees. As noted above, Applicant is not required to provide each and every piece as to how to make and use the claimed invention, for the gaps can be filled by the knowledge of a skilled person in the art or routine experimentation. *See* Chiron Corp. v. Genetech, Inc., 363 F.3d 1247. The aforementioned prior art references have consistently supported the use of CpG to invoke a Th1 response both *in vitro* and in animal models, a common mechanism of action that contributes to the therapeutic effects of CpG oligonucleotides. These references have also demonstrated the promising therapeutic effect of immunostimulatory

CpG oligonucleotides in treating diseases such as asthma and allergy. Moreover, data presented in the specification, including the use of a CpG oligonucleotide for the treatment of allergic asthma in a murine model, also teaches how to make and use the claimed invention. In light of the prior art, as well as the disclosure of the instant application, one skilled person in the pertinent art would have known how to administer CpG-ODNs to a subject to treat allergic disorders by stimulating a Th1 immune response via routine experimentation. Thus the enablement requirement under 35 U.S.C. § 112 has been satisfied. *See* In re Johnson, 282 F.2d 370, 373.

Further, actual reduction to practice prior to filing is not required to satisfy the enablement requirement. *See* Gould v. Quigg, 822, F.2d 1074, 1078. MPEP 2164.02 also makes it clear that lack of working example or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the ground of lack of enablement. Accordingly, lack of a working example of the claimed invention should not be a per se bar to patentability for lack of enablement.

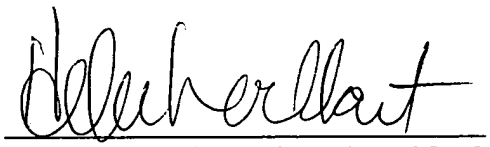
In view of the foregoing, the office action does not provide persuasive reasons that a skilled person in the art would need undue experimentation to make and use the claimed invention. Thus, withdrawal of the rejection of claim 19 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Arthur M. Krieg, Applicant(s)

By: 

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